patients are likely to have some of these same concerns but do not speak of them, and therefore are not relieved of some fear or need to know. At the very least physicians should be aware of the nature of the most requested topics in the Tel-Med experience, and sensitive to any indication of need for information on these subjects by their patients.

—MSMW

More Effective Use of Antidepressants

ELSEWHERE IN THIS ISSUE appears a Medical Progress article, "Recent Advances in Antidepressant Drug Treatment," by Stephen E. Ericksen, MD.

Antidepressant drugs were not enthusiastically received during their first decade of use. Controlled comparisons of both tricyclics and monoamine oxidase (MAO) inhibitors either showed no difference from placebo or a trivial one, as many depressed patients remitted spontaneously. I summarized this literature in a 1966 editorial entitled "Antidepressants: A Somewhat Depressing Scene."[1] In retrospect, this pessimism was unwarranted due to two errors that were even then being recognized.

The heterogeneity of depressive reactions was a major problem. Although a plethora of terms denote the various types of depressions, most early studies assumed that antidepressants were universally effective. Failure to show differences between antidepressant drugs and placebo was common in studies using unselected groups of depressed patients. This difficulty was partially resolved by the recognition that patterns of symptoms and signs of depressed patients could be used to make diagnostic distinctions. This approach led to identification of a subgroup of depressed patients who responded specifically to tricyclic antidepressants.[2] Not surprisingly, these patients had characteristics resembling those of so-called endogenous depressions, a group that had been reported as specifically responsive in the initial clinical trial of imipramine.[3]

Most clinicians now agree that tricyclics are specifically effective in endogenous depression. Whether such selectivity applies to MAO inhibitors is less certain. The high success rate of the latter drugs in neurotic depressions is clouded by the high rate of placebo response found in this group. Anecdotal evidence suggests that patients with depressions characterized by high levels of anxiety, hypochondriasis and obsessive-compulsive-phobic features may respond specifically to MAO inhibitors, as noted in Dr. Ericksen's paper. Such selectivity of action of MAO inhibitors has been difficult to assess because these agents are not commonly used in clinical practice.

Biochemical classification of depressions has been recently attempted. Both serotonin and norepinephrine may be involved in the amine hypothesis of depression, some investigators favoring one transmitter, others, the other. This dilemma has been neatly solved by suggesting that a functional deficiency of both noradrenergic and serotonergic neurotransmission may be involved in endogenous depression. Distinctions are made by the pattern of excretion of the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). This metabolite is more derived from central nonadrenergic activity than any other urinary metabolite of norepinephrine, such as normetanephrine or vanilmandelic acid. *Low* excretion of MHPG is presumed to represent deficient nonadrenergic activity, while *high* excretion is believed to represent deficient serotonergic activity. Reciprocal levels of the serotonin metabolite, 5-hydroxy-indoleacetic acid and MHPG in cerebrospinal fluid also suggest such a relationship.

The importance of making distinctions between the two neurotransmitter subtypes of depression hinges upon the idea that various tricyclics differ in selectively blocking uptake of these two neurotransmitters. Amitriptyline is at present the most specific blocker of uptake of serotonin while desipramine is most selective in blocking uptake of norepinephrine. The appeal of MHPG determinations as a way to classify depressions is based on the possibility that the most efficacious drug for any given patient might be predated. Although preliminary data suggest this to be the case, they are still fragmentary.[4]

Unfortunately, MHPG excretion is no different in patients with affective disorders than in normal persons. The usual daily excretory rate, both in depressed patients as well as in normal persons, usually ranges between 900 and 3,500 μg per 24 hours.[5] Such values account for more than 90 percent of these reported in patients with affective disorders. One can think of no other precedent in all of medicine in which a diagnostic classification

of patients can be made on the basis of variations within the normal range of values for a laboratory test.

A second reason for the disappointing early results with antidepressant drugs was probably inadequate doses. As clinical experience developed it became apparent that in some, although by no means in all, patients a daily dose of 150 mg or more of imipramine or amitriptyline was needed to obtain optimal effects. Likewise doses of the MAO inhibitor, phenelzine, in the order of 60 to 90 mg per day are required for full therapeutic effect. Many of the early studies of these drugs used smaller doses, ones that would be only partly efficacious, if at all.

Determination of plasma concentration of tricyclic antidepressants has been proposed as a way to assure adequate dosage. For a variety of reasons, the same dose of tricyclic antidepressant may produce widely different steady-state plasma concentration of drug among different persons. It is still not certain whether or not a therapeutic range of plasma concentrations can be established for these drugs. Nortriptyline, although not widely used, has been most extensively studied. A therapeutic range of 50 to 150 ng per ml has been proposed for that drug. Imipramine has been less intensively studied, but the present feeling is that plasma concentrations less than 120 to 150 ng per ml of combined imipramine/desipramine (most of the drug is converted to its secondary amine metabolite) are likely to be ineffective.[6]

Such correlations between clinical effects and plasma concentrations are confounded by a number of problems. First, tricyclics are highly protein-bound so that slight shifts in the degree of protein-binding may vastly alter the amount of pharmacologically active, unbound drug even *with no change in total plasma concentration.* Second, many of the drugs produce hydroxylated metabolites which retain pharmacological activity. In the case of nortriptyline, the 10-hydroxy metabolite is usually more abundant than the parent drug. The assumption that the hydroxy metabolites are conjugated, and therefore inactive, may not be true. Third, technical problems of how the blood samples are obtained and how much contact they have with the stoppers of tubes may produce inconsistent artifacts in determination of plasma concentrations of nortriptyline.

Determination of plasma concentrations of tricyclic antidepressants should probably best be done on a selective basis rather than as a routine monitoring. The following indications are suggested:

- Failure of a patient to respond to doses in the range of 75 to 150 mg per day. A very low plasma concentration may suggest poor bioavailability or, more likely, non-compliance.
- A decision to use larger than usual doses, such as those greater than 250 mg per day. Having some record of drug levels shows a proper degree of concern about such intensive treatment.
- Treatment of very old or very young patients should be conservative. Such patients have decreased protein-binding of tricyclics and more unbound, active drug. Plasma concentrations should be deliberately kept on the low side in such patients. Older patients also tend to get higher peak and steady-state levels, possibly because they clear the drug less rapidly.
- The presence of concurrent illness that may interfere with drug clearance, such as liver disease, would merit checking plasma concentrations. An illness that may be seriously aggravated by the drug, such as heart disease, might also merit determination of plasma concentrations, although one may prefer electrocardiographic monitoring.
- Plasma concentration may help explain some questionable adverse reactions.
- The decision about when an overdosed patient is fully recovered may be helped by determining if the plasma concentration of drug has returned to the therapeutic range.

With careful attention to the diagnosis of depression, it is likely that antidepressant drugs may be used in fewer patients but with better results. By using adequate doses of these drugs, one may eliminate a major cause of treatment failures. These are the major lessons we have learned in how to use these drugs more effectively.

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